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Clusters provide a better holistic view of type 2 diabetes than simple clinical features

Although we were very pleased to see the strong replication of our original clustering study[1] by John Dennis and colleagues,[2] we disagree in part with their conclusions for the following reasons.

For the past 100 years, diabetes has been diagnosed by measuring one metabolite, glucose. However, type 2 diabetes progression is clearly more complex than the contribution of this one variable. Diabetes develops when a person can no longer increase insulin secretion to meet the increased demands imposed by insulin resistance; therefore, including measures of insulin secretion and action in the definition of the disease is logical. Our cluster-based classification identified three severe and two milder forms of type 2 diabetes.[1]

Importantly, by extrapolating from type 1 diabetes on diabetic complications, clinicians have been misled to think that microangiopathic complications (retinopathy, neuropathy, and nephropathy) develop together in type 2 diabetes, as seen in type 1 diabetes, but this is not the case. Retinopathy and neuropathy are prevalent in patients with severe insulin-deficient diabetes whereas nephropathy and fatty liver are more common in patients with severe insulin-resistant diabetes.[3] Complications associated with severe insulin-resistant diabetes are difficult to prevent solely by lowering blood glucose concentration in these patients because of their good metabolic control, but their insulin sensitivity should be improved.

Dennis and colleagues[2] question the clinical usefulness of subclassifying type 2 diabetes and suggest that purpose-specific models with simple quantitative measures (ie, age at diagnosis) predicts changes in HbA_{1c}, and that baseline kidney function predicts a decline in estimated glomerular filtration rate (eGFR), better than clusters do. However, our study[1] provided a wealth of information beyond that of Dennis and colleagues' study,[2] primarily insights into the pathogenesis of type 2 diabetes and information on disease progression and outcomes. Nevertheless, Dennis and colleagues[2] do provide valuable information on the response to different treatments. They evaluated the HbA_{1c}-lowering effect of three antidiabetic medications (metformin, sulfonylurea, and the insulin-sensitiser rosiglitazone) in the ADOPT and RECORD trials.[4,5] In line with our prediction, rosiglitazone had the largest effect in patients with severe insulin-resistant diabetes. Rosiglitazone had no effect in patients with severe insulin-deficient diabetes suggesting that these patients might need insulin or a glucagon-like peptide-1 receptor agonist.

The study by Dennis and colleagues does have some limitations that should be considered when interpreting the results. First, the strict inclusion criteria pertaining to HbA_{1c}, fasting glucose, eGFR, BMI, and age in the ADOPT and RECORD trials affect the results. In fact, applying the same inclusion criteria to the ANDIS cohort assessed in our study[1] excludes 90% of patients with severe insulin-deficient diabetes and 50% of those with severe insulin-resistant diabetes—many of the patients with the most severe disease. Second, although it was encouraging to see that the decline in eGFR could still be replicated, the absence of replication after adjustment for initial eGFR should not be over-interpreted, especially as this analysis had a short follow-up in patients with a less rapid decline in eGFR. Another problem ensues from using the nearest centroid method on scaled data from cohorts with different inclusion criteria without adjusting for the differences in mean and SD.

We found that the statement "clusters are non-aetiological, overlapping, highly dependent on the variables used to classify them, and cannot robustly be defined at an individual level"[2] was not well substantiated. We agree that clusters can be partially overlapping, especially for individuals in the periphery of the clusters. However, using genetics, we have already shown that aetiological differences between clusters exist.[1] Although the severe autoimmune diabetes cluster, which is insulin-deficient, is strongly associated with variants in the *HLA* locus (as in type 1 diabetes), no such association was seen for the non-autoimmune severe insulin-deficient diabetes cluster (which showed association with a variant in the *TCF7L2* gene known to be associated with type 2 diabetes). The severe insulin-resistant diabetes cluster showed none of these genetic features.

Clusters can be defined on an individual level, as shown in our study.[1] We have also developed a tool based on machine learning, which we think could be used in the clinic to estimate the probability that an individual patient belongs to a specific subgroup. This tool also identifies the next best match, which helps in cases of partially overlapping clusters. In our view, the clustering (which has been replicated almost all over the world [including China, Germany, and the USA])[3,6] provides a more holistic view of type 2 diabetes and a better platform for precision medicine than simple clinical features.

We declare no competing interests.

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Authors' reply

We thank Emma Ahlqvist and colleagues for their comments on our study,[1] itself a follow-up to their original paper,[2] which proposed five novel subgroups of adult-onset diabetes based on data-driven cluster analysis.

We agree that our analysis was restricted to assessing the clinical utility of the clusters and did not assess any broader insights into the pathophysiology of type 2 diabetes or the cause of complications arising from the clustering approach. The potential insights into the pathophysiology of complications in type 2 diabetes are exciting and we look forward to hearing more about this in future publications. We accept that the models we propose are constructed to accurately predict clinical outcomes and do not readily lead to pathophysiological insights.

In our opinion, the individual data from clinical trials used in our study offer considerable advantages over population-based cohorts for the assessment of optimal treatment and clinical utility. In clinical trials, treatment groups are randomly allocated and follow-up is done at set times and is protocol-driven, thereby providing robust information on treatment responses and clinical outcomes. We agree that clinical trials represent only a subgroup of the total population with diabetes, with the selection of specific patients having a disproportionate effect on some of the clusters; however, it is interesting that the proportion of individuals allocated to each cluster in the trial data were similar to those described in population cohorts.

In our view, precision medicine approaches in type 2 diabetes are likely to have the greatest effect on clinical practice if based on simple and reproducible clinical measures available in any diabetes clinic.[3] The proposed approach based on five clusters[2] is limited because it requires homoeostatic model assessment measures at diagnosis, based on fasting glucose and either fasting insulin or C-peptide concentration, which are rarely measured in the clinic. Variability of the precision of fasting insulin or C-peptide assays provide an additional barrier to the use of homoeostatic model assessment measures in the clinic.[4,5] By contrast, our approach used only routine clinical measures (BMI, age at diagnosis, HbA_{1c}, and renal function), and showed that, when modelled continuously, these simple measures outperform the more complex five clusters to select treatment and predict disease progression.

In conclusion, we think the approach used should depend on the outcome you want. Exciting new insights into the cause of diabetes complications might arise from data-driven approaches to classification, such as the five clusters proposed by Ahlqvist and colleagues.[1] However, for practical approaches to personalising type 2 diabetes care, models making use of an individual's precise clinical measures are likely to be more useful than classification approaches based on clinical measures to assign individuals to subgroups. In summary, a need for both approaches exists because they have different roles. The final arbitrators of the most useful approach will be the clinicians who need to select treatment or predict likely outcomes.

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Lifestyle intervention and impaired glucose tolerance in the Da Qing study

We write in response to the report of the 30-year results of the Da Qing Diabetes Prevention Outcome Study,[1] which showed that lifestyle intervention for people with impaired glucose tolerance (IGT) is effective to curb the onset of type 2 diabetes and its consequences.

Because the Da Qing trial was initiated in the 1980s, long before the introduction of current WHO diabetes criteria, these results need to be interpreted cautiously. The IGT